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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO. |
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| 09/050,249 | 03/30/98 | OKAMURA | OKAMURA-2P |

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| EXAMINER | |
|---|---|
| FITZGERALD, D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | 13 |

DATE MAILED: 05/25/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 03 MARCH 2000

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE (3) month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) 56, 59-88 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☒ Claim(s) 81-84 is/are allowed.
☒ Claim(s) 56, 59-80, 85-88 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☒ received in Application No. (Series Code/Serial Number) 08/502,535.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

**1.** Applicant's amendments have obviated the rejection previously set forth under 35 U.S.C. § 112, second paragraph (¶ 6 of the Office action mailed 6 October 1999, Paper No. 10).

Insofar as the rejections of record are maintained below, applicant's arguments filed 3 March 2000 have been fully considered, but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**2.** The terminal disclaimer filed on 3 March 2000, disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,912,324, has been reviewed and is accepted. The terminal disclaimer has been recorded.

In view of the disclaimer, the nonstatutory double patenting rejection over the claims of the '324 patent (¶ 5) is withdrawn as moot.

**3.** The following observations are made with respect to the amended claims.

Applicant has amended the claims to recite "IL-18" concurrently with "IGIF." This amendment is consonant with the examiner's amendment of the title in the parent application, serial no. 08/502,535, now U.S. Patent No. 5,912,324. As noted there, IL-18 is the current art-recognized name for the material described in the disclosure as IGIF. As the terms are no more than labels for the same material described identically in the disclosure and must be thus construed in the claims, the use of "IL-18" does not constitute new matter.

Claims 67, 68, 73, and 80 are susceptible of unambiguous construction with reference to the limitations the dependent claims impose on "the IGIF protein" because the antecedent for that "protein" is clear in context. As a formal matter, however, the wording is consonant with that used in base claim 59 to describe the reference IGIF species to which the monoclonal antibody binds. The examiner suggests that the dependent claims would be more readable if amplified to more clearly signal that "the IGIF protein" to which the limitations apply is not that reference species. Claims 67 and 68, for example, could be amended to recite an "active IGIF protein" at all instances; and claims 73 and 80, "the IGIF protein in the immune complex."

**4.** The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**5.** Claims 59-80, 89, 90, and 92, are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the invention as now claimed. This rejection concerns the sufficiency of the written description with respect to the subject matter claimed. See the Commissioner's Revised Interim Guidelines published 21 December 1999 at 64 F.R. 71427-71440.

The question of possession of the claimed antibodies and methods employing them turns on a determination as to possession of the IGIF proteins for which the antibodies are specific. The amended claims no longer require that the IGIFs be both of murine origin and closely related in structure to the exemplified murine IGIF having the sequence of SEQ ID NO: 2. They are thus generic to IGIF proteins meeting the broad functional limitation of independent claims 59 or 92 and various structural or biochemical limitations recited in various combinations in the dependent claims.

To determine whether there is correspondence between the generic invention of the claims and the written description, is necessary to determine whether the description conveys to one skilled in the relevant art that applicant was in possession of the claimed genus at the time the application was filed. To this end, it is appropriate to inquire whether a number of species representative of the genus are described in complete structural terms or, alternatively, with reference to other identifying characteristics, *e.g.*, partial structure, chemical properties, functional properties, *etc.* What constitutes a "representative number" of species for any given genus depends in part on whether the level of skill in the art, the teachings in the disclosure, or teachings in the prior art establish a correlation between the structural, functional, or other identifying properties characteristic of the genus.

All of the various genera claimed are represented by two molecular species described with particularity in the disclosure, the $Met^{70}$ and $Thr^{70}$ isoforms of SEQ ID NO: 2. No other IGIF species meeting the limitations of the claims, either naturally occurring (splice variants, allelic

variants, species homologs, products of related genes in a gene family, *etc.*) or non-natural (substitution variants, deletion or truncation variants, *etc.*), all of which would be embraced by the language of the claims, are identified or particularly described. The amended claims are tolerant of significant structural dissimilarity as compared to the exemplified IGIFs, and the limitations which are positively recited have not been shown to correlate with the biological activity required by claims 59 and 92. Neither would the skilled artisan reasonably expect, for example, that a molecular weight of 19 ± 5 kDa, a pI of 4.8, or a requirement for the presence of short subsequences affording *ca.* 30% overall identity with SEQ ID NO: 2 would correlate with the retention of biological properties characteristic of the murine IGIF described in the disclosure. The Office therefore concludes that the two isoforms of SEQ ID NO: 2, differing by only a single amino acid, are not representative of the genera of IGIFs recited in claims 59-80, 89, 90, and 92, and thus that the disclosure does not convey to those skilled in the art that the inventors were in possession of the genera of monoclonal antibodies specific for such IGIFs at the time the application was filed.

**6.** Claim 91 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide a repeatable method for obtaining monoclonal antibody M-1, and it does not appear to be a readily available material. The particular mAb is a unique material which will not necessarily or predictably be produced identically by replicating of the methods described in the specification. The mAb is required to practice the invention of claim 91 because the claim expressly requires it. Deposit of the M-1 hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112.

**If a deposit is made under the terms of the Budapest Treaty,** then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating

(a) that the deposit has been made under the terms of the Budapest Treaty; **and**

(b) that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent,

would satisfy the deposit requirements. See 37 C.F.R. § 1.808.

**If a deposit is not made under the terms of the Budapest Treaty,** then the requirements may be satisfied by an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or by a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and establishing that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 C.F.R. § 1.807 is provided; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function described in the manner in the specification.

**In either case,** the identifying information set forth in 37 C.F.R. § 1.809(d) should be added to the specification if it is not already present. For deposits made with the ATCC, note that effective 23 March 1988 the depository's address is:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

See 37 C.F.R. §§ 1.803-1.809 for additional explanation of these requirements.

**7.** Claims 85-88 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakamura *et al.* (*Infect. Immun.*, 1993) in light of the concessions made during the prosecution of the parent of this application for the reasons stated at ¶ of Paper No. 10.

Claim 85 remains rejected on these grounds because a polyclonal antiserum raised against the Nakamura 75 kDa IGIF material will inherently comprise antibodies specific for the 19 kDa polypeptide of SEQ ID NO: 2, and the claim is tolerant of the presence of components which do not specifically recognize SEQ ID NO: 2. Claims 86-88 remain rejected because the prior art IGIF material comprises the recited SEQ ID NO: 2 polypeptide, and the method of claim 86 is tolerant of the presence of other materials in the immunogen.

Applicant first argues that only with hindsight would one have known that the 19 kDa IGIF species was present in the Nakamura 75 kDa material. This argument is irrelevant because the

obviousness of the invention does not rely on any knowledge of the components present in the prior art material.

It is further urged that not all mAbs raised against the 75 kDa material would necessarily recognize the 19 kDa polypeptide. This argument is not relevant to the claims to polyclonal antisera because the evidence of record indicates that antibodies having the recited specificity would necessarily be present in an antiserum raised against the prior art material, notwithstanding that other antibodies would also be present.

**8.** The rejection under 35 U.S.C. § 103 based upon Nakamura is withdrawn as to claims 56 and 59-84. On the singular facts of this case, a conclusion of obviousness or non-obviousness turns more on the legal analysis applied than on the evidence adduced on this record. As noted previously, the prior art describes an IGIF material which inherently comprises the 19 kDa mIGIF described in the instant disclosure. Application of the statements made by counsel in the parent file to the facts of this case compels the conclusion that the generic invention of monoclonal antibodies and the subgeneric invention of neutralizing monoclonal antibodies specific for the Nakamura 75 kDa material have been conceded to be obvious. It is critical here to distinguish these generic inventions from the inventions of all of the species within the genera; applicant has not fairly conceded that any such specific inventions are likewise obvious.

The legal question at issue is whether the present claims are patentable over the generic and subgeneric inventions taken, for purposes of argument, to be provided by the prior art. The examiner considers that the analysis here must first invoke the question of whether the genera of monoclonals specific for the Nakamura IGIF material "anticipate" any of the claims to monoclonal antibodies presented in this application. That is, the subject matter conceded to be obvious should be treated as though it were set forth in a single prior art reference and analyzed with respect to the standards of § 102. Under the law of inherency, a reference cannot anticipate a claim unless there is no possibility, as determined (in *ex parte* examination) by a preponderance of the evidence, that the purportedly anticipatory embodiment(s) fail to necessarily meet all of the material and functional limitations of the claim. *See, e.g., Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1365, 52 U.S.P.Q.2d 1303 (Fed. Cir. 1999). Here, applicant has argued (in effect) that the subgenus of neutralizing mAbs specific for the Nakamura IGIF material could include some which recognize epitopes on the "non-IL-18" polypeptide or epitopes, *e.g.*,

conformational epitopes, which form in the 75 kDa complex but not in the monomeric 19 kDa IGIF. The examiner finds this line of argument scientifically plausible, and there is no evidence on this record which effectively refutes it. The preponderance of the evidence thus favors the finding that all of the members of the subgenus of neutralizing mAbs specific for the prior art IGIF material would not necessarily meet the limitations of the instant "monoclonal" claims.

The next question involves the more conventional "obviousness" analysis under § 103. Here there is ample objective evidence which supports a conclusion of non-obviousness. As evidenced, for example, by Dinarello *et al.*, *J. Leukocyte Biol.* 63: 658-64 (1998), cited for the record, IL-18 is now known to have a number of useful properties which were not appreciated at the time of the instant invention. The unexpected advantages attaching to IL-18 *per se* accrue as well in favor of the claims to mAbs specific for it. Moreover, one ordinarily skilled in this art would without fail choose the 19 kDa IL-18 in preference to the Nakamura 75 kDa IGIF material as an immunogen to generate any IL-18-specific monoclonal. Thus notwithstanding some (likely substantial) overlap between the generic inventions conceded to be obvious and the inventions of the present claims, the claims patentably define over the prior art as taken in view of counsel's concessions.

The examiner notes that the "clean" copy of the Nakamura paper and applicant's explanatory remarks at pages 11-12 of the reply filed 3 March 2000 resolve the issue of whether an active low molecular weight band is in fact identified in the reference.

**9.** The art cited but not relied upon is pertinent to identifying the components of the Nakamura 75 kDa material. Kim *et al.*, *PNAS* 97: 1190-95 (2000), describes isoforms of a recently identified IL-18-binding protein. Because this protein neutralizes IL-18 almost quantitatively, the examiner considers it unlikely that the biologically active material described by Nakamura represents a stoichiometric complex of IL-18 and any of the IL-18BP isoforms described by Kim. Torigoe *et al.*, *JBC* 272: 25737-42 (1997), describes a transmembrane receptor for IL-18. Insofar as the examiner is aware, a soluble receptor corresponding to the Torigoe receptor has not been described in the research literature.

**10.** The examiner believes that he has addressed all pertinent arguments. Claims 81-84 are allowed.

As allowable subject matter has been indicated, Applicant's response must either comply with all formal requirements or specifically traverse each requirement not complied with. In particular, **formal drawings are required in response to this Office action.** See 37 C.F.R. § 1.111(b) and § 707.07(a) of the M.P.E.P.

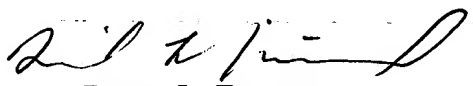
**11.** Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

*A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED. ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(A) WOULD THEN BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.*

**12.** Any inquiry concerning this communication should be directed to David Fitzgerald, who can be reached by any of the following means:

| | |
|---|---|
| Telephone | (703) 308-3934 |
| Fax | |
| All formal papers | (703) 308-4242 |
| Informal communications | (703) 308-0294 |
| e-mail (note PTO policies below) | david.fitzgerald@uspto.gov |

Inquiries of a general nature should be directed to the Technology Center 1600 receptionists at (703) 308-0196.



DAVID L. FITZGERALD
PRIMARY EXAMINER
ART UNIT 1646

24 May 2000

The **best time to reach Examiner Fitzgerald** is from 9 a.m. to 4 p.m. (Eastern). If he cannot take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, the supervisor for this Art Unit, Gary Kunz, may be reached at (703) 308-4623.

Most official papers and all informal **communications may be submitted to the PTO by fax.** For specific policies, refer to 37 C.F.R. § 1.6 and the notice published at 1096 O.G. 30. To facilitate their receipt and handling, please —

- Call the examiner when you send an urgent communication.
- **Do not send a duplicate copy** by mail or courier.

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